bjh guideline

The diagnosis and management of primary autoimmune haemolytic anaemia

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Scope

The objective of this guideline is to provide healthcare professionals with guidance on the management of patients with primary autoimmune haemolytic anaemia (AIHA). The guidance may not be appropriate to every patient and in all cases individual patient circumstances may dictate an alternative approach.

Attempts to categorise autoimmune haemolytic anaemia (AIHA) and define its response to treatment vary considerably in the published literature. Author defined criteria have been used in this guideline, but this limits study comparisons and will have contributed to differences in reported outcome. The investigation and diagnosis of adult and paediatric AIHA are considered together. Guidance on the treatment of adult AIHA is then followed by a section on paediatric AIHA.

Methodology

Literature review details. Recommendations are based on the systematic review of published English language literature from January 1960 to October 2015 (see Appendix S1 for further details). Although recommendations are unchanged, an expanded version of this guideline is available as Appendix S2.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the British Committee for Standards in Haematology (BCSH) guidance pack (http://www.bcshguidances.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html) and the GRADE working group website http://www.gradeworkinggroup.org

Working group membership. The guideline group was selected to be representative of UK-based experts in the diagnosis and management of AIHA.

Review. Review of the manuscript was performed by the BCSH General Haematology Task Force, BCSH Executive Committee and then a sounding board of the British Society for Haematology (BSH). This compromises 50 or more members of the BSH who have reviewed this Guidance and commented on its content and applicability in the UK setting.

Background

AIHA is a decompensated acquired haemolysis caused by the host's immune system acting against its own red cell antigens. The incidence is approximately 1 per 100 000/year (Pirofsky, 1975; Klein *et al*, 2010). It can occur at any age but incidence rises with increasing age. Serologically, cases are divided into warm type (65%), cold type (29% cold haemagglutinin disease [CHAD], 1% paroxysmal cold haemoglobinuria) or mixed AIHA (5%). Approximately half are primary (idiopathic) AIHA and half are secondary to associated disorders (Table I).

Patients with AIHA may present with symptoms of anaemia (weakness 88%, dizziness 50%, dyspnoea 9%), haemolysis (jaundice 21%, dark urine 3%) or symptoms of an underlying disorder (Pirofsky, 1975). Without underlying disease, examination may be unremarkable or reveal mild pallor or splenomegaly. Less often, severe haemolysis leads to hepatosplenomegaly, haemoglobinuria and signs of heart failure (Packman, 2008).

Cold haemagglutinin disease (CHAD) can present as a primary chronic clonal disorder, usually occurring in middle age or in the elderly. Cold-induced acrocyanosis (dusky blue appearance of toes, fingers, nose tip or ears) or Raynaud phenomenon occur in 40–90% of patients (Berentsen *et al*, 2006; Swiecicki *et al*, 2013). Secondary CHAD can be self-limiting, for example following childhood infection. With its different

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Table I. Classification of autoimmune haemolytic anaemia.

Warm AIHA
Primary
Secondary
Neoplasia (CLL, Lymphoma, Solid organ)
Infection (e.g. Hepatitis C, HIV, CMV, VZV, Pneumococcal infection, Leishmaniasis, Tuberculosis)
Immune dysregulation
Connective tissue disorders (e.g. SLE, Sjögren syndrome, Scleroderma)
Ulcerative colitis, PBC, Sarcoidosis
Post transplantation
Immune deficiency syndromes (e.g. CVID)
Cold AIHA
Cold Haemagglutinin Disease
Primary
Secondary
Malignancy (e.g. CLL, NHL, Solid organ)
Infection (e.g. Mycoplasma, Viral infections, including IM)
Autoimmune disease
Post-allogeneic HSCT
Paroxysmal Cold Haemoglobinuria
Primary
Secondary
Infection (e.g. Adenovirus, Influenza A, Syphilis, CMV, IM, VZV, Measles, Mumps, *Mycoplasma pneumoniae, Haemophilus influenzae*, *E. coli*)
Mixed type AIHA
Primary
Secondary
Lymphoma, SLE, Infection

AIHA, autoimmune haemolytic anaemia; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; CVID, common variable immunodeficiency; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplantation; IM, infectious mononucleosis; NHL, non-Hodgkin lymphoma; PBC, primary biliary cirrhosis; SLE, systemic lupus erythematosus; VZV, varicella zoster virus.

natural history, secondary CHAD has also been termed cold agglutinin syndrome (Berentsen & Tjonnfjord, 2012).

Paroxysmal cold haemoglobinuria (PCH) is typically transient, presenting 1–2 weeks after an upper respiratory tract infection or other childhood illness with acute fever, abdominal, back or leg pain and haemoglobinuria (Gehrs & Friedberg, 2002). Haemolysis can be severe and intravascular but usually settles over several weeks.

Diagnostic approach to suspected AIHA

When a patient presents with suspected AIHA, three questions should be considered. Is there haemolysis; is the haemolysis autoimmune and what is the type of AIHA?

Is there haemolysis?

Typical laboratory findings in patients with haemolysis:

- Bilirubin (unconjugated) - increased
- Reticulocyte count - increased
- Lactate dehydrogenase (LDH) – may be normal or increased
- Haptoglobin – reduced
- Blood film – spherocytes, agglutination or polychromasia
- Urinalysis/dipstick test positive for blood but urine microscopy negative for red cells - if haemolysis is intravascular, leading to haemoglobinuria
- Urinary haemosiderin - can be detected approximately 1 week after onset of intravascular haemolysis

However, there may be confounding factors as these laboratory tests are not highly specific. Some parameters may be normal, especially with mild compensated haemolysis.

The differential diagnosis of haemolytic anaemia is shown in Table II.

Table II. Differential diagnosis of haemolytic anaemia.

Hereditary
Membrane disorders (e.g. HS, HE)
Enzyme disorders (e.g. G6PD, PK deficiency)
Haemoglobinopathies (e.g. SCD, Unstable haemoglobins)
Acquired
Immune
Autoimmune (e.g. Warm or cold AIHA)
Alloimmune (e.g. HDN, HTR, post-allogeneic HSCT)
Drug induced
Non-immune
Infection (e.g. Malaria, *Clostridium perfringens*)
Mechanical (e.g. Prosthetic heart valve)
PNH
TMA (e.g. TTP, HUS)
Hypersplenism
Oxidant substances (e.g. Dapsone, Arsine gas, Amyl nitrite)
DIC
Severe burns
Extracorporeal circuits
Renal failure

AIHA, autoimmune haemolytic anaemia; DIC, disseminated intravascular coagulation; G6PD, Glucose-6-phosphate dehydrogenase deficiency; HDN, haemolytic disease of the newborn; HE, hereditary elliptocytosis; HS, hereditary spherocytosis; HSCT, haematopoietic stem cell transplantation; HTR, haemolytic transfusion reaction; HUS, haemolytic uraemic syndrome; PK, pyruvate kinase; PNH, paroxysmal nocturnal haemoglobinuria; SCD, sickle cell disease; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Is the haemolysis immune?

A positive direct antiglobulin test (DAT) indicates the presence of immunoglobulin (Ig)G, IgM, IgA or complement (usually C3d) bound to the red cell membrane. In the presence of haemolysis, this suggests an immune aetiology but clinical assessment is required before a diagnosis of AIHA can be made. Typically monospecific anti-IgG and anti-C3d

antibodies are used in the initial screening and these help to determine the type of AIHA.

A positive DAT is not specific and is also associated with a wide range of non-haemolytic disease states, possibly through passive deposition of immunoglobulins or immune complexes; examples include liver disease, chronic infection, malignancy, systemic lupus erythematosus (SLE), renal disorders and drugs such as intravenous immunoglobulin (IVIg) or antithymocyte globulin.

The DAT: Recommendation

- **At a minimum, the DAT should include monospecific anti-IgG and anti-C3d (1C)**

DAT positive, evidence of haemolysis. Before diagnosing AIHA, ask the following 5 questions:

- Is there a history of blood transfusion in the last 3 months?
  - o Consider a delayed haemolytic transfusion reaction (HTR)
- Has the patient received a solid organ or allogeneic haematopoietic stem cell transplant (HSCT)?
  - o Consider alloimmune haemolysis caused by major ABO mismatch (HSCT) or passenger lymphocyte syndrome (PLS) (solid organ or HSCT).
- In infants, could this be haemolytic disease of the newborn (HDN)?
- Has the patient received any relevant drugs?
  - o Consider drug-induced immune haemolytic anaemia (DIIHA).
- Is there another known cause of haemolysis?
  - o Given the high prevalence of an incidental positive DAT within the hospital population, consider whether there is an alternative cause of haemolysis or abnormal laboratory values

DAT-negative AIHA

Rarely, AIHA patients test negative with a tube test DAT, for example due to a low affinity antibody, low levels of red cell bound antibody or an immunoglobulin not tested for (e.g. IgA-only AIHA). A gel column agglutination method is a more sensitive method that is less prone to error than a conventional tube test (Fayek *et al*, 2012). AIHA can be diagnosed in 3% of patients testing negative with a gel card method by using a red cell elution technique (Sachs *et al*, 2006). The Donath-Landsteiner test may be considered in children with haematuria and is discussed under investigations. Patients with DAT-negative AIHA generally have a milder anaemia and are steroid responsive.

Investigation of DAT-negative haemolysis: Recommendation

- **In patients with unexplained haemolysis and a negative screening DAT, retest with a column agglutination DAT method that includes monospecific anti-IgG, anti-IgA and anti-C3d (1B). If also negative, consider preparing and investigating a red cell eluate (2C).**

Investigations

The most relevant tests to investigate for an underlying cause for AIHA are shown in Table III. Although reticulocytopenia can occur in the acute phase of AIHA; haematinic deficiency, marrow infiltration, aplastic anaemia and parvovirus B19 infection should be considered if it is present. Further serological investigation is required to determine the type of AIHA (e.g. warm, CHAD, PCH) as the approach to treatment differs. Finally, if the patient requires blood, investigations are needed to exclude underlying alloantibodies and identify units suitable for transfusion. In adults, two 7 ml EDTA samples are usually sufficient for initial serological investigation. A clotted sample is also required for investigation of suspected PCH or DIIHA.

What type of AIHA is present?

Typical serological characteristics of AIHA subtypes are shown in Table IV. Although the autoantibody specificity can sometimes be identified, specificity does not help predict the clinical outcome (Issitt, 1985).

Warm AIHA. Is caused by autoantibodies (usually IgG) that bind red cells optimally *in vitro* at 37°C. When tested with anti-C3 and anti-IgG reagents, the DAT would be positive for: IgG only (35%), IgG + C3 (56%) or C3 only (9%) (Issitt, 1985). AIHA can be considered warm when there is a consistent clinical picture and a DAT positive to IgG, C3 or both, when a clinically significant cold reactive antibody has been excluded (Fig 1).

CHAD. Is caused by autoantibodies (usually IgM) that bind red cells optimally *in vitro* at 4°C. Although the DAT is usually positive for C3 only, 21–28% are also positive with IgG (Berentsen *et al*, 2006; Swiecicki *et al*, 2013). Furthermore, only 7–31% of patients with AIHA and a C3-only positive DAT have CHAD.

Marked red cell agglutination on the blood film is classically seen in CHAD but can occur in mixed AIHA and PCH. Milder agglutination sometimes occurs in warm AIHA and

Table III. Investigations in patients presenting with autoimmune haemolytic anaemia (AIHA).

Primary evaluation	
Haemolytic screen	
FBC, blood film, LDH, haptoglobin, bilirubin, DAT, reticulocyte count ± urine for haemosiderin or urine dipstick and microscopy	
Detection of underlying disorders (investigation of AIHA)	
Serum Igs and electrophoresis with immunofixation*	
HIV, HBV, HCV	
Anti-dsDNA, ANA	
CT chest, abdomen and pelvis	
Additional investigation in selected patients with AIHA	
Bone marrow examination:	CHAD, age ≥60, features in history, examination, FBC or film suggesting possible marrow infiltration
U&E, LFT, clotting, BP, urine dipstick:	If pregnant or thrombocytopenic, to exclude DIC or pregnancy-associated TMA
Infection screening:	Dependent on symptoms, travel history and age (see Table I)
Peripheral T-cell subsets, creatinine, LFT, clotting:	All children and if suspected Evans syndrome
Parvovirus, haematinics:	If reticulocytopenia
Additional serological investigation in selected patients with AIHA	
Direct agglutination test (DAggT)	If DAT positive for C3 ± IgG
Cold antibody titre	If DAggT positive
Monospecific DAT for IgM, G, A, C3	If DAT-negative AIHA suspected
Red cell eluate	If (monospecific) DAT- negative AIHA suspected
Donath-Landsteiner	If DAT is positive for C3 ± IgG and i)DAggT negative or insignificant CAs and ii)age <18 years or haemoglobinuria or cold associated symptoms or atypical serology
Cold autoagglutinin thermal amplitude	If clinical significance of cold autoagglutinin unclear

ANA, antinuclear antibody; BP, blood pressure; C3, complement component 3; CHAD, cold haemagglutinin disease; CT, computerised tomography; DaggT, direct agglutination test; DAT, direct antiglobulin test; DIC, disseminated intravascular coagulation; dsDNA, double-stranded DNA; EBV, Epstein Barr virus; FBC, full blood count; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; Igs, immunoglobulins; LDH, lactate dehydrogenase; LFT, liver function tests; TMA, thrombotic microangiopathy; U&E, urea and electrolytes.
*If a cold autoantibody suspected, keep sample at 37°C until serum has been separated.

Table IV. Serological features of AIHA and cold agglutinins.

	Warm AIHA	Mixed AIHA	CAs	CHAD	PCH
Typical DAT	IgG or IgG + C3	IgG + C3	Negative	C3	C3
Antibody specificity	Usually a high incidence antigen. ~3% have specificity (e.g. anti-e, anti-E or anti-c)	Warm IgG usually lacks specificity. The cold antibody may be anti-I, anti-i or lack specificity	Usually anti-I	Usually anti-I (~90%), sometimes anti-i, rarely anti-Pr	Usually anti-P
Antibody titre (at 4°C)	Not applicable	Cold antibody may have a low titre (<1:64)	Usually <1:64	Usually >1:500 but can be less	Usually <1:64
Thermal amplitude	Bind optimally at 37°C	Usually ≥30°C	Usually <25°C	Usually ≥30°C	Usually <20°C

AIHA, autoimmune haemolytic anaemia; CAs, cold agglutinins; CHAD, cold haemagglutinin disease; DAT, direct antiglobulin test; PCH, paroxysmal cold haemoglobinuria.

clinically insignificant polyclonal cold agglutinins (CAs) can cause agglutination on a blood film spread at room temperature. Up to 35% of patients with warm AIHA have CAs reactive at 20°C (Petz & Garratty, 1980).

CHAD must therefore be distinguished from insignificant CAs. The thermal amplitude of CAs (the maximum temperature at which antibody binds red cells *in vitro*) is usually <25°C. At 4°C, the CA antibody titre is usually only positive with a dilution <1:64 and it rarely exceeds 1:256. In CHAD, the titre is usually >1:500 at 4°C and the thermal amplitude ≥30°C (but can be as low as 25°C if red cells are suspended in saline rather than 30% bovine albumin). Defining an absolute cut-off for titre or thermal amplitude is difficult and there are exceptions.

CHAD can be diagnosed in patients with AIHA and a DAT positive to C3 ± IgG, with a consistent clinical picture and a high titre cold reactive antibody. The thermal amplitude may be considered as a supportive serological investigation where diagnostic uncertainty exists.

Primary CHAD. The term 'primary' CHAD has been used to describe patients without other systemic autoimmune disease or infective aetiology and who have no clinical or radiological evidence of underlying lymphoma. However, with immunophenotyping, the majority of such cases have evidence of a clonal bone marrow lymphoproliferative disorder and a circulating IgM monoclonal paraprotein (Berentsen, 2011). The paraprotein can be detected by serum electrophoresis and immunofixation in >90% of cases (Berentsen *et al*, 2006) but the sample must be kept at 37°C until the serum has been separated or the antibody will remain bound to red cells. All cases of suspected primary CHAD should be reviewed by an appropriately constituted haemato-oncology multidisciplinary team (National Institute for Clinical Excellence, 2003).

Paroxysmal cold haemoglobinuria (PCH). PCH is caused by a biphasic IgG antibody that binds to red cells at low temperature and causes complement-mediated lysis as the temperature is raised. The DAT is usually positive to C3 only. There may be agglutination, spherocytes or erythrophagocytosis by neutrophils on the blood film. Reticulocytopenia is common early in PCH, evolving into reticulocytosis with recovery. PCH can be diagnosed in patients with AIHA and a positive Donath-Landsteiner test. The test can be technically difficult (Sokol *et al*, 1999) and false negative results can be avoided by using an indirect method. Testing should be performed by a specialist laboratory and a warm separated serum sample is required. Testing should be considered in patients with AIHA and a DAT positive for C3 ± IgG, when CHAD has been excluded, and there is either haemoglobinuria, cold-associated symptoms, atypical serological features or if the patient is <18 years old. The DAT is negative in some cases of PCH. The Donath-Landsteiner test should therefore also be considered in children with haemolysis, haemoglobinuria and a negative DAT.

Mixed AIHA. Mixed AIHA is caused by a combination of a warm IgG antibody and a cold IgM antibody with a thermal amplitude of at least 30°C. The DAT is usually positive with IgG and C3. The cold antibody may have a low antibody titre (e.g. <1:64). Cold-induced haemolysis, Raynaud phenomenon or acrocyanosis do not appear to be features of mixed AIHA (Sokol *et al*, 1983; Shulman *et al*, 1985). Mixed AIHA can be diagnosed in patients with AIHA, a DAT positive for IgG and C3, a cold antibody with a thermal amplitude ≥30°C, evidence of a warm IgG antibody and the absence of typical features of CHAD.

Diagnostic pathway

A diagnostic pathway is illustrated in Fig 1. Patients with AIHA and a DAT positive for C3 ± IgG should be screened for a cold antibody. A direct agglutination test (DAggT) can be performed as a screening test in the local transfusion laboratory; a clinically significant cold haemagglutinin can be excluded if saline-suspended normal red cells are not agglutinated by the patient's serum after incubation at room temperature for 30–60 min (Petz, 2008). If this screening is positive, further testing is needed to distinguish insignificant CAs from CHAD. Samples for titres and thermal amplitude should be kept at 37°C for transportation. As this can be challenging, received ethylenediaminetetra-acetic acid (EDTA)-anticoagulated samples should be warmed to 37°C in a water bath for 1 h before testing (Issitt, 1985).

Limitations. The diagnostic algorithm (Fig 1) is a guide and the diagnosis is not always straightforward. The clinical picture should be considered and the advice of a reference laboratory may be required before a final diagnosis is made. A limitation of serological testing (cold antibody titres, thermal amplitude and the Donath-Landsteiner test) is the current absence of a UK External Quality Assurance (EQA) scheme. Testing should therefore be conducted in laboratories performing these tests on a regular basis.

Identifying the type of AIHA: Recommendations

- **Patients with AIHA and a DAT positive for C3 ± IgG should be screened for a cold antibody using a direct agglutination test (DAggT) at room temperature (1C)**
- **Patients with a positive cold autoantibody screen should be further investigated with an antibody titre in a laboratory performing these tests on a regular basis (2C). Received EDTA-anticoagulated samples should be warmed to 37°C in a water bath for 1 h prior to removal of the plasma for testing (1C).**
- **In patients with suspected CHAD, the clotted sample for protein electrophoresis and immunofixation should be kept at 37°C until the serum has been separated (1C).**
- **All cases of suspected primary CHAD should be reviewed by an appropriately constituted haemato-oncology multidisciplinary team (1C)**

Serological investigation of patients requiring transfusion

Investigation should be guided by sections 6·5 and 7·13 of recent BCSH guidelines on pre-transfusion compatibility procedures (Milkins *et al*, 2013). The main aims of the investigation are to determine ABO, Rh and K status of the patient and identify alloantibodies, if present.

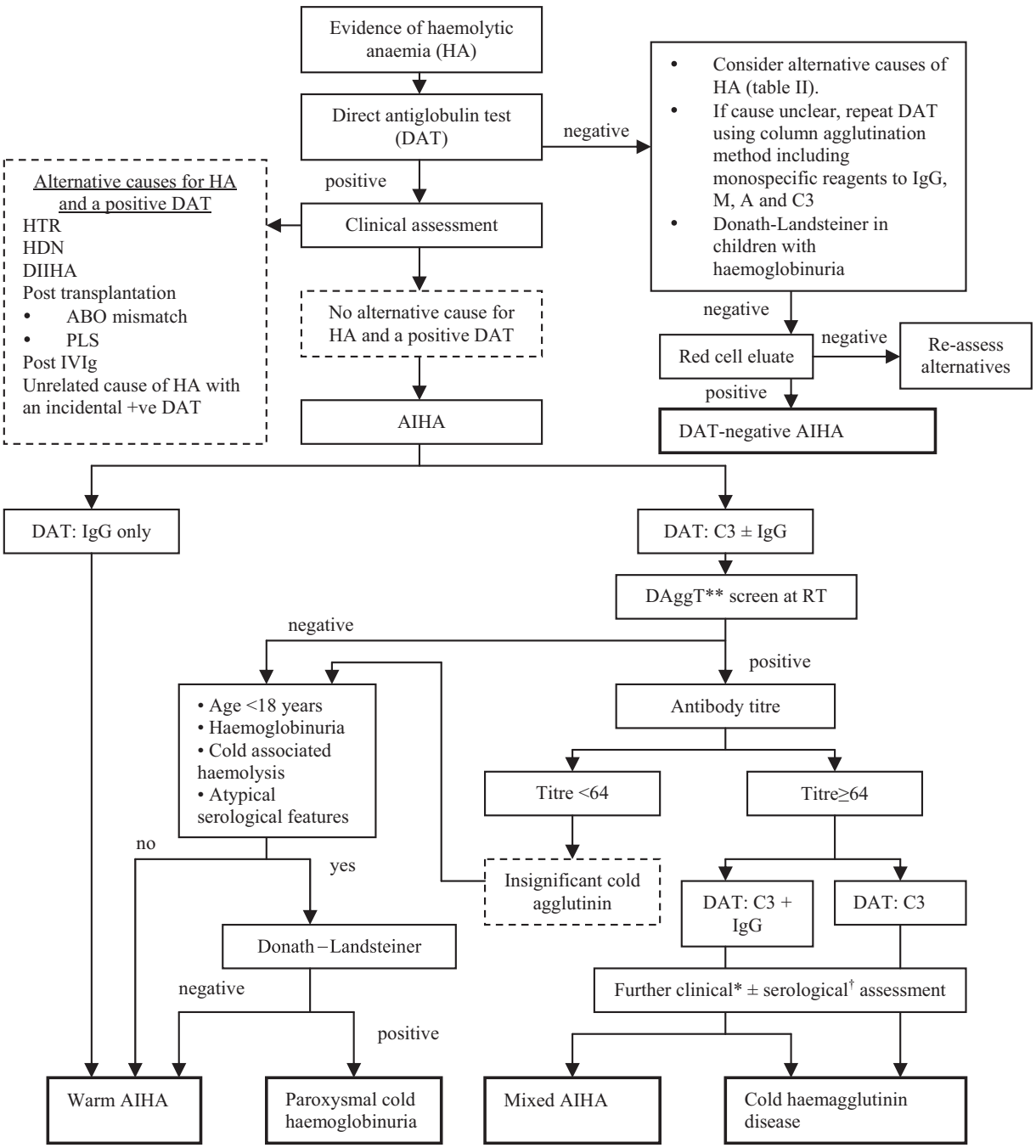

Fig 1. Diagnostic pathway for AIHA. AIHA, autoimmune haemolytic anaemia; CHAD, cold haemagglutinin disease; DAggT, direct agglutination test; DAT, direct antiglobulin test; DIIHA, drug-induced immune haemolytic anaemia; HA, haemolytic anaemia; HDN, haemolytic disease of the newborn; HTR, haemolytic transfusion reaction; IVIg, intravenous immunoglobulin; PLS, passenger lymphocyte syndrome; RT, room temperature. *The final diagnosis of CHAD or mixed AIHA is based on the overall clinical picture, including supportive serological findings. †For example the thermal amplitude. **Saline suspended red cells and patient's serum at room temperature for 30–60 min.

Rescue (emergency) therapy

General Strategies for all AIHA

- Investigations may reveal a treatable underlying cause, such as infection.
- If drug-induced AIHA is suspected, relevant medication should be stopped.

Blood transfusion. Full compatibility testing can take 4–6 h or more (Petz, 2004). Approximately 30% of patients with

AIHA have an underlying alloantibody (most commonly Rh or K) but these are rare if there is no history of previous transfusion or pregnancy (Petz, 2004). If anaemia is life threatening, transfusion with ABO, Rh and K matched blood is more appropriate than delaying until full serological investigations have been completed. In patients with a clinically significant cold type antibody, the use of a blood warmer and ensuring a warm environment for transfusion is rational although the evidence of benefit is limited.

Transfusion: Recommendations

- **If anaemia is life threatening in the time required for full compatibility testing, transfuse with ABO, Rh and K matched red cells (1C)**
- **Consider the use of a blood warmer for transfusion in patients with cold AIHA (CHAD, mixed AIHA and PCH) (2C)**

Warm AIHA

These are the options available in an emergency situation:

Immunoglobulins. Evidence from case series suggests that 40% of patients respond to IVIg 0·4–0·5 g/kg/day for 5 days and most responders maintained their Hb for ≥3 weeks (Flores *et al*, 1993). Response was predicted by low pre-treatment Hb; and IVIg is accepted in the UK Department of Health guidelines as a short term treatment when the Hb is <60 g/l (but higher in patients with co-morbidities) or as a temporising measure prior to splenectomy (Wimperis *et al*, 2011).

Plasma exchange. The evidence for plasma exchange is largely limited to case reports and any benefit is temporary. Plasma exchange has been used in patients with severe haemolysis while attempting control with other therapies, such as immunosuppression (Von Baeyer, 2003; Szczepiorkowski *et al*, 2010).

Methylprednisolone. The experience of high dose intravenous methylprednisolone is limited to case reports. Methylprednisolone may have a role in fulminant cases but the risk of serious infections may also increase (Everett *et al*, 2006; Bay *et al*, 2007).

Emergency splenectomy and splenic embolisation. Patients with severe transfusion-dependent haemolysis who have not responded to immunosuppression may require urgent splenectomy. If the patient is not vaccinated 2 weeks prior to splenectomy, this should be deferred until 14 days post-splenectomy as functional antibody responses are improved (Davies *et al*, 2011). In critically ill patients with warm AIHA deemed unfit for splenectomy (e.g. severity of anaemia or lack of available blood to transfuse), case reports have documented success with partial splenic embolisation.

Rescue therapy - warm AIHA: Recommendation

- **Consider IVIg or plasma exchange for severe or life threatening anaemia (2C)**

Primary CHAD

These are the options available in an emergency situation:

Steroids. The overall response of CHAD to steroids can be disappointing with response rates of 14–69% in larger series. Responses are often partial, and cannot be sustained without an unacceptably high steroid dose. However, given limited therapeutic options, a trial of prednisolone 1 mg/kg/day may be considered as a rescue therapy.

Plasma exchange. Responses were seen in 4/6 case reports (Von Baeyer, 2003). However, responses are often transient (Petz, 2008) and like warm AIHA, its role may be in stabilising patients with severe disease in conjunction with alternative therapy. Agglutination can occur within the cell separator and its tubing, especially if the agglutinin is active at 37°C and the room and extracorporeal circuit may need a high temperature setting. Daily or alternative day exchange of 1–1·5 times plasma volume with albumin has been recommended (Szczepiorkowski *et al*, 2010).

Rescue therapy – Primary CHAD: Recommendation

- **Consider plasma exchange or steroids for severe or life-threatening anaemia (2C)**

Non-emergency management

General strategies

Venous thrombo-embolism (VTE) prophylaxis. VTE is an important cause of morbidity and mortality in AIHA and is more likely when haemolysis is active. In one study of patients with severe AIHA (defined as Hb <85 g/l), VTE occurred in 6/28 (21%), and was significantly more likely if no thromboprophylaxis was given (Hendrick, 2003). In another study, VTE occurred in 8/40 (20%): seven had uncompensated haemolysis (Hb range 41–89 g/l) and 6 were outpatients (Lecouffe-Desprets *et al*, 2015).

Thromboprophylaxis: Recommendation

- **Thromboprophylaxis with low molecular weight heparin is recommended for in-patients with an acute exacerbation of haemolysis (1C) and should be considered in**

ambulatory patients during severe exacerbations (Hb <85 g/l) (2C)

Folic acid. Prior to the widespread practice of folic acid supplementation, numerous cases of megaloblastic anaemia and folate deficiency were reported in patients with chronic haemolytic anaemia.

Folic acid: Recommendation

- **Patients with AIHA should receive folic acid supplementation (1B)**

Gastric 'protection'. The incidence of peptic ulcer disease (PUD) in the general population is approximately 0·1%, with risk of upper gastrointestinal complications increasing 2·2- to 4·2-fold with corticosteroids. Other risk factors include increasing age, and previous ulcer. In patients receiving corticosteroids, the highest risk is in those receiving concomitant non-steroidal anti-inflammatory drugs (NSAIDS) or aspirin while previous history of PUD may also increase risk.

Gastric 'protection': Recommendation

- **Patients receiving corticosteroids who are at increased risk for peptic ulcer disease e.g. concomitant thrombocytopenia, prior history peptic ulcer disease, concurrent use of non-steroidal anti-inflammatory drug (NSAID), anticoagulant or antiplatelet agent and age ≥60 years, should receive a proton pump inhibitor (2C)**

Prevention of glucocorticoid induced osteoporosis. Osteoporotic (particularly vertebral) fracture occurs in up to 30–50% of adults receiving long term glucocorticoids (Rizzoli *et al*, 2012). Calcium and vitamin D supplements (typically 1200–1500 mg calcium and 800–1000 units vitamin D) reduce bone loss and are recommended for all patients receiving corticosteroids (Weinstein, 2011; Rizzoli *et al*, 2012). In well-performed studies, bone mineral density was increased by bisphosphonates. Postmenopausal women and men aged ≥50 years starting corticosteroids with an anticipated duration ≥3 months at a dose of prednisolone ≥7·5 mg/day are considered high risk for osteoporotic fracture and additional treatment such as a bisphosphonate is recommended (Grossman *et al*, 2010; Hansen *et al*, 2011; Lekamwasam *et al*, 2012).

Osteoporosis prevention: Recommendations

- **All patients should receive oral calcium and vitamin D supplements while taking corticosteroids (1A)**
- **Postmenopausal women and men age ≥50 years commencing corticosteroids should receive a bisphosphonate when treatment is anticipated to be ≥3 months at a dose of prednisolone ≥7·5 mg/day (1A)**

Specific management strategies

These are summarised in Fig 2. For many patients, AIHA is a chronic condition and the goal of therapy is disease control with minimal side effects. Patients with mild compensated haemolysis may not require active therapy. Morbidity and mortality are poorly understood, but while death from uncontrolled haemolysis can still occur, the relative contribution of infection in patients on immunosuppression is significant.

Primary warm AIHA

First line treatment. Corticosteroids—Approximately 80% of patients respond to corticosteroids at a dose equivalent to prednisolone 60–100 mg/day and approximately two-thirds achieve complete remission (CR). The initial response may take several weeks but absence of response by 21 days should be considered a steroid failure. In responding patients, an incremental taper can begin, for example once Hb >100 g/l or after a maximum of 3 weeks, reducing to 20–30 mg over 4–6 weeks, and then by 5 mg every month. In a series of 33 primary AIHA cases, relapse was more common if steroids were tapered to ≤10 mg in less than 2 months and if stopped in less than 6 months (Dussadee *et al*, 2010). Approximately 20% of patients remain in remission after steroids are discontinued. Although a further 40% can maintain an acceptable Hb on maintenance prednisolone <15–20 mg, due to the long term side effects of steroids, second line therapy should be considered.

Dexamethasone Data are limited but do not suggest that dexamethasone is superior to prednisolone (Meyer *et al*, 1997; Ionita *et al*, 2010).

Primary warm AIHA - first line treatment: Recommendations

- **First line therapy is prednisolone 1 mg/kg/day (1B)**
- **Second line therapy should be considered if (2C):**
  - **No response to 1 mg/kg/day after 3 weeks**
  - **Relapse during or after steroid reduction**

Second line treatment. The best-studied and most efficacious treatments used are rituximab and splenectomy. Approximately 70% of cases respond to splenectomy but even higher response rates are reported with rituximab. Following splenectomy, refractory or relapsing patients often require immunosuppression and the rate of serious infection appears higher post-splenectomy (Rivero *et al*, 1979; Barcellini *et al*, 2014; Roumier *et al*, 2014). Given the significance of infection and chronic course of AIHA, most patients will benefit from an effective well-tolerated steroid-sparing agent prior to consideration of splenectomy.

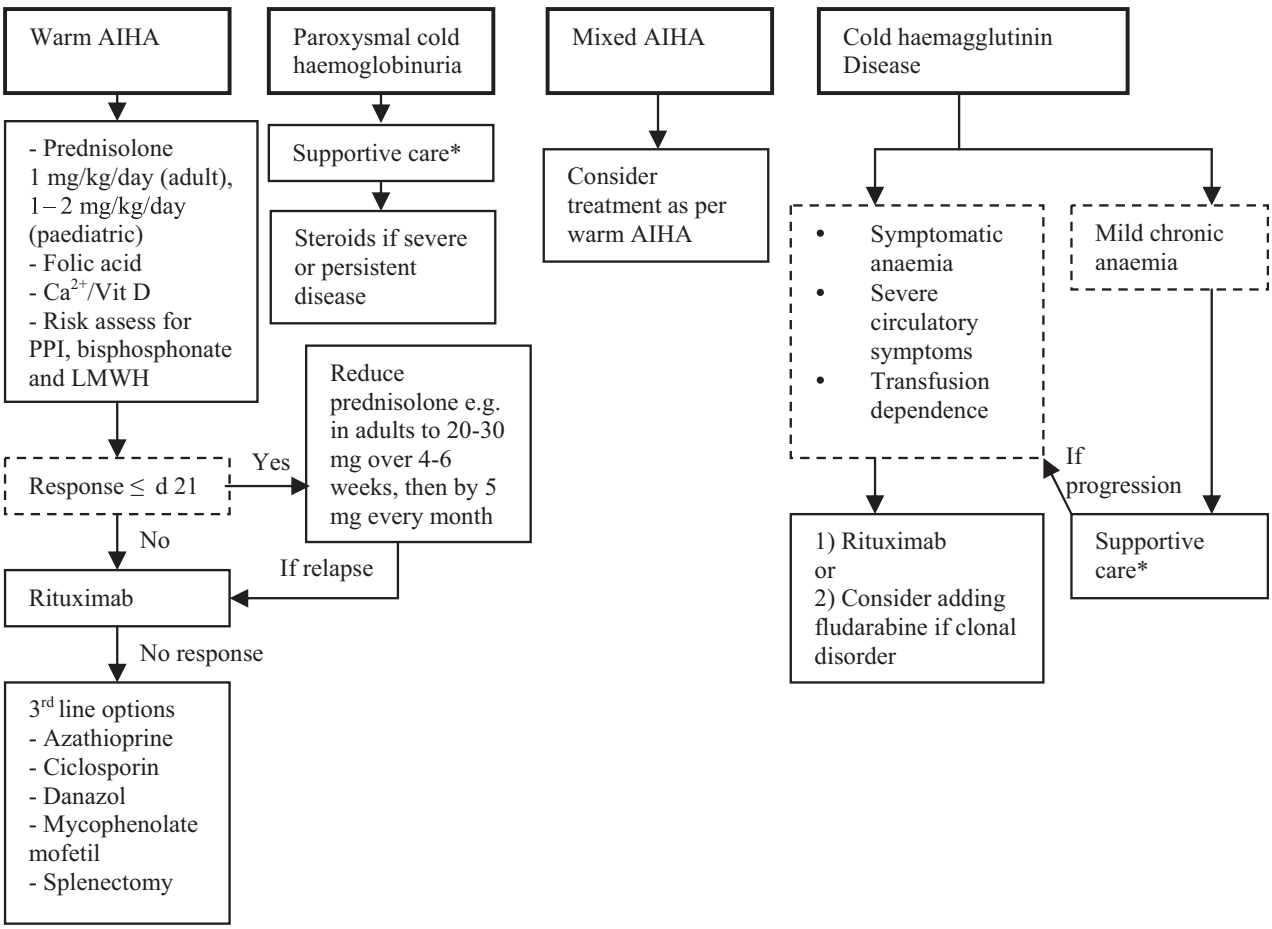

Fig 2. Therapeutic pathway for primary AIHA. Ca^{2+}/Vit D, Calcium/Vitamin D; ≤day 21, within 21 days; FBC, full blood count; LMWH, low molecular weight heparin; PPI, proton pump inhibitor. *keep warm, avoid active cooling, folic acid, monitor FBC +/− transfusion

Rituximab—Response rates of 100% have been reported following rituximab for primary warm AIHA [n = 17/17 (Bussone *et al*, 2009); n = 11/11 (D'Arena *et al*, 2007); n = 14/14 (Barcellini *et al*, 2012)]. In series including primary and secondary warm AIHA, 79% responded with CR in 42% (Reynaud *et al*, 2015). Prior splenectomy does not adversely affect outcome, although better outcome is associated with shorter duration of AIHA. In the only prospective randomised study, first line rituximab and prednisolone was compared to prednisolone monotherapy (Birgens *et al*, 2013). At 12 months, CR rates were 75% vs. 36% (P = 0·003) respectively.

Median time to response is approximately 3–6 weeks (range 2–16 weeks). The long term remission rate is unknown but relapse occurs in 14–25% after a median of 15–21 months (Bussone *et al*, 2009; Barcellini *et al*, 2012) and in 50% by 30 months (Maung *et al*, 2013). Rituximab is largely well tolerated although severe neutropenia, transient infusion-related reactions (Bussone *et al*, 2009) or infections have been reported. Reactivation of hepatitis B virus (HBV) is a potentially fatal complication and pre-administration screening with serology for HBV surface antigen and HBV core antibody is recommended (https://www.medicines.org.uk/emc/medicine/2570; last accessed 1 April 2014). Progressive multifocal leucoencephalopathy is a rare complication (Carson *et al*, 2009).

The standard regimen is 375 mg/m^2 weekly for four consecutive weeks but low dose rituximab achieves profound B cell suppression when used for autoimmune disorders (Provan *et al*, 2007). Rituximab 100 mg weekly for 4 weeks with prednisolone, first or second line (Barcellini *et al*, 2012), produced comparable response rates. However, rituximab was used at an earlier disease stage than studies of standard dose therapy, and variable definitions of response and short follow-up further limit comparison.

Primary warm AIHA - second line treatment: Recommendation

- **Rituximab (1B)**

Third line treatment. The treatment options are listed alphabetically so as to show no preference for a particular therapy.

Azathioprine—Approximately 60% of AIHA patients respond to azathioprine 100–200 mg/day (Worlledge *et al*, 1968), 2–2·5 mg/day with prednisolone (Pirofsky, 1975) or dose unstated (Barcellini *et al*, 2014; Roumier *et al*, 2014). However, the number achieving steroid independence and the duration of response is unclear. Thiopurine methyltransferase (TPMT) deficiency prevents azathioprine metabolism and should be excluded prior to commencing therapy.

Ciclosporin—Case reports and small series suggest some efficacy in AIHA. Where specified, the ciclosporin dose was typically 5 mg/kg/day.

Danazol—Six out of 7 patients with primary warm AIHA (3 treated first line) responded to danazol 200 mg 3–4 times/day, added to prednisolone (Ahn *et al*, 1985). The series was later expanded to 13 with a 77% response rate (Ahn, 1990). In a further study, 3/3 patients with secondary AIHA responded to danazol 200 mg three times daily (Manoharan, 1987).

Mycophenolate (MMF)—Small series and case reports suggest some efficacy in primary and secondary AIHA. Most patients had received multiple previous therapies and were treated with MMF 500 mg twice daily, titrated up to 1 g twice daily. Responses typically took 3–4 months.

Splenectomy—Larger series of unselected patients with AIHA suggest 50–85% of patients respond (improved Hb or increased sensitivity to steroids). Response rates appear higher in primary vs. secondary AIHA. If the series are combined, 71% (61/86) of primary warm AIHA cases responded to splenectomy (Chertkow & Dacie, 1956; Dausset & Colombani, 1959; Allgood & Chaplin, 1967; Ly & Albrechtsen, 1981; Akpek *et al*, 1999) with a CR rate of 42% (31/74). Most responses occur within the first few months of surgery but slower responses (5–6 months) have been reported. Approximately a third of patients relapse after splenectomy.

Radioisotope scanning—Although early studies suggested that relatively high splenic uptake would predict a good response to splenectomy, this was not supported by subsequent studies and scanning has fallen from routine clinical practice.

Infection—Vaccinations and the re-vaccination schedule should be based on the latest Department of Health (Public Health England, 2013) or equivalent guidelines. Prophylactic antibiotics should be started postoperatively and a course of antibiotics for emergency use provided at discharge (Davies *et al*, 2011).

Thrombosis—Approximately 2% of unselected patients develop VTE within 90 days of splenectomy with higher risk in those with haemolytic anaemia (Thomsen *et al*, 2010). Postoperative portal or splenic vein thrombosis (PSVT) is also more common in those with haemolytic anaemia, occurring in 8% (4/47) of one series (van't Riet *et al*, 2000). Extended low molecular weight heparin (LMWH) prophylaxis has been proposed on grounds of risk (Mohren *et al*, 2004) but evidence of benefit is lacking. Longer term VTE risk is also increased by AIHA and splenectomy.

Primary warm AIHA - third line treatment: Recommendations

- **Azathioprine, ciclosporin, danazol, mycophenolate mofetil, splenectomy (2C)**

Patients with AIHA undergoing splenectomy: Recommendations

- **Radioisotope studies to determine the main site of red cell destruction are not currently recommended when considering splenectomy (1C)**
- **Patients should be counselled on infection risk and be vaccinated at least 2 weeks before splenectomy (1C).**
- **There should be a low threshold for investigating patients with post-operative fever, abdominal pain or ileus with Doppler ultrasound to exclude portal or splenic vein thrombosis (1B)**
- **Patients without a contra-indication should receive thromboprophylaxis with low molecular weight heparin (LMWH) following splenectomy (1C). Extended prophylaxis following discharge may be considered in patients considered high risk (2C).**
- **After splenectomy, patients should be discharged on prophylactic antibiotics, provided with a course of antibiotics for emergency use and given advice on risk factors for infection. Long-term follow-up should be organised for revaccination in primary or secondary care (1C).**

Treatment options for patients failing third line therapies.

Alemtuzumab—Case reports suggest some efficacy in AIHA although dosing regimens have varied (see Appendix S2).

Cyclophosphamide—Although some success has been reported with low dose oral cyclophosphamide (e.g. 50–100 mg daily) with or without prednisolone, there are few data on dosing or efficacy and, given its mutagenic potential, oral cyclophosphamide cannot be recommended over second line steroid-sparing agents. Higher intravenous doses also appear effective, for example 50 mg/kg/day for 4 days (Moyo *et al*, 2002) or 1 g monthly for 4 months (Thabet & Faisal, 2014).

Haematopoietic stem cell transplantation (HSCT)—Given that toxicity and treatment-related mortality is significant, HSCT should be restricted to carefully selected patients with

refractory life-threatening disease following multidisciplinary review. Fewer than 20 patients treated for AIHA have been reported to the European Group for Blood and Marrow Transplantation (EBMT). Some prolonged remissions have been reported, particularly with allogeneic HSCT (Passweg & Rabusin, 2008). Procedures should be performed in Joint Accreditation Committee of ISCT and EBMT (JACIE)-accredited centres with expertise in HSCT for patients with autoimmune diseases.

Warm AIHA caused by IgA antibodies

Warm AIHA caused by isolated IgA occurs in 0·1–2·7% of cases and usually responds to conventional treatment including steroids and splenectomy.

Primary warm AIHA caused by IgA antibodies: Recommendation

- **The therapeutic approach to warm AIHA is unaffected by identification of warm IgA antibodies (concurrent with IgM, IgG or as an isolated cause of AIHA) (2C).**

Mixed AIHA

Mixed AIHA is usually described as causing severe haemolysis (Grant *et al*, 1988). Approximately 50% are primary while secondary cases are often associated with SLE. Mixed AIHA is steroid responsive but most often leads to chronic haemolysis. Splenectomy was unsuccessful in 3/4 (Sokol *et al*, 1983) and 2/3 patients (Shulman *et al*, 1985). Occasional success has been reported with IVIg and plasma exchange for acute haemolysis, with chemotherapy for underlying lymphoma and with cyclophosphamide.

Mixed AIHA: Recommendations

- **First line therapy for mixed AIHA is prednisolone 1 mg/kg/day (1C)**
- **If AIHA is secondary, optimize treatment of the underlying disorder (1C).**
- **If AIHA is primary, consider immunosuppression as second line therapy similar to primary warm AIHA (2C).**

Primary CHAD

For all patients, avoid cold exposure where possible to reduce the risk of severe exacerbations, dressing to protect the head, face and distal extremities in cold weather. Therapeutic intervention should be considered for symptomatic anaemia, severe circulatory symptoms or transfusion dependence (Berentsen & Tjonnfjord, 2012).

In patients requiring treatment, splenectomy has usually been avoided because IgM sensitised red cells are not selectively removed in the spleen. Evidence of efficacy is therefore lacking and splenectomy appears to have a very limited role.

Pharmacological treatment. CHAD is less responsive than warm AIHA. Case reports or small series do not encourage the use of chlorambucil, cladribine, azathioprine or cyclophosphamide. Alpha interferon was effective in some but not all case reports. Case reports also document a response to eculizumab (Roth *et al*, 2009), bortezomib (Carson *et al*, 2010) and rituximab-bendamustine (Gueli *et al*, 2013).

Rituximab—In prospective studies, the overall response rate to rituximab 375 mg/m^2 weekly for 4 weeks was 51% (27/53) [n = 4/6 (Berentsen *et al*, 2001), n = 14/27 (Berentsen *et al*, 2004), n = 9/20 (primary and secondary CHAD) (Schollkopf *et al*, 2006)] and treatment was well tolerated. However 57–89% relapsed with a median response duration of 6·5–11 months. In a prospective study of rituximab combined with fludarabine, the response rate was 76% and estimated median response duration >66 months although 44% had grade 3–4 haematological toxicity (Berentsen *et al*, 2010).

Treatment of primary CHAD: Recommendations

- **Patients should be advised to avoid cold exposure where possible (1C)**
- **Indications for treatment: symptomatic anaemia, severe circulatory symptoms or transfusion dependence (1C)**
- **First line treatment: rituximab, or if clonality has been demonstrated, the addition of fludarabine may be considered (1B)**

Surgery in patients with CHAD and cold agglutinins

Iatrogenic cooling, such as peri- and post-operative hypothermia, can precipitate haemolysis in CHAD patients. Surgery can proceed safely by careful maintenance of body temperature. Knowing the antibodies thermal amplitude may help define a minimum temperature threshold. Elective surgery should be deferred if a transient post-infective CHAD is suspected.

Cardiothoracic surgery on cardiopulmonary bypass (CPB) may involve paralysis and cooling of the heart to 8–12°C (cold cardioplegia). Clinically insignificant CAs might then become significant. In patients with CHAD or CAs identified pre-operatively, a number of successful strategies, such as warm cardioplegia with systemic normothermia have been employed. Agglutination can also present intraoperatively with increased pressure in the cardioplegia line (Bracken *et al*, 1993; Fischer *et al*, 1997) or with visible agglutination in the cardioplegia system. However, complications appear rare in patients with CAs undergoing CPB, even without modifications to reduce hypothermia (Jain *et al*, 2013) and

although serological screening prior to cold cardioplegia is recommended by some, it is not currently routine practice.

CHAD, Cold agglutinins and surgery: Recommendations

- **In patients with CHAD, take measures to ensure the patient is normothermic during and immediately after surgery (1C)**
- **All cardiothoracic units should have a policy for CA screening prior to cold cardioplegia and for management of unexpected agglutination detected during cold cardioplegia (2C)**

Childhood AIHA

AIHA can occur at any age during childhood from infancy through to adolescence but with a peak incidence <5 years. In up to 77% of cases it is a self-limiting illness, requiring only short term therapy (Buchanan *et al*, 1976). Warm AIHA predominates in children followed in frequency by PCH, typically triggered by a viral infection. CHAD is less common in children compared to adults, and often follows a mycoplasma infection. Immunological disease (most commonly Evans syndrome or CVID) is associated with approximately 50% of cases.

Clinical and laboratory features

Most children present with pallor, jaundice, tiredness or dark urine. Less commonly, there will be fever or abdominal pain and 3% presented with collapse, coma or acute renal insufficiency due to sudden, severe anaemia (Aladjidi *et al*, 2011). The laboratory investigations and differential diagnosis are described in the adult section above and in Tables II and III. In the differential diagnosis, particular attention should be given to congenital disorders, such as Diamond-Blackfan anaemia, transient erythroblastopenia of childhood and parvovirus B19 infection. Autoimmune lymphoproliferative syndrome and a primary immunodeficiency should be specifically tested for before commencing steroids or IVIg. Investigations should include serum immunoglobulins, peripheral T cell subsets and antinuclear antibodies. An unusual association is giant cell hepatitis (GCH) and liver function tests should also be checked (Maggiore *et al*, 2011).

Management

The management of AIHA in children is similar to that described in the adult sections above. First line therapy is corticosteroids, typically given as prednisolone at a starting dose of 2 mg/kg/day (Habibi *et al*, 1974; Heisel & Ortega, 1983; Naithani *et al*, 2007) with responses in 81–100% of children with primary or secondary AIHA. As children compensate better for a falling Hb, blood transfusion support can be less aggressive until there is evidence of cardiac decompensation, which is unusual when the Hb is >50 g/l (Ware & Rosse, 1998). IVIg may be a useful rescue therapy and, in one series, 6/11 (54·5%) children responded to doses of 0·4–2 g/kg/day for 2–5 days (Flores *et al*, 1993).

The best-studied second line agent is rituximab, with response rates of 75–100% in children with primary or secondary AIHA. A response to splenectomy was reported in 3/4 (Buchanan *et al*, 1976), 3/4 (Sokol *et al*, 1984) and 12/12 (8 CR, 4 PR) (Habibi *et al*, 1974) children. However, there was little detail on durability of response while in another series of five patients, none achieved CR but three died of sepsis within a year of splenectomy (Heisel & Ortega, 1983). Given that childhood AIHA is often self-limiting, splenectomy should usually be considered a third line treatment option. Small series and case reports suggest that azathioprine, ciclosporin and danazol may also have some activity in childhood AIHA. In a recent study, 4/4 children responded to sirolimus given as second/further-line treatment for primary AIHA (Miano *et al*, 2015).

Childhood AIHA: Recommendations

- **Transfusion can usually be avoided unless there are signs of cardiac decompensation (2C)**
- **Test for additional immunological diseases before starting treatment (1A).**
- **Investigations should also include liver function tests (2C).**

Paroxysmal cold haemoglobinuria

The most common form of PCH is acute and transient, following an infectious illness in childhood. PCH may account for up to 40% of AIHA in younger children. Although the original cases of PCH were described in patients with late stage or congenital syphilis, chronic cases are now usually idiopathic or follow infection.

Precipitating factors

Most cases in children have a clear history of a precipitating upper respiratory infection. Infectious precipitants described include varicella, adenovirus, cytomegalovirus, Epstein–Barr virus, *Haemophilus influenzae*, *E. coli*, *M. pneumoniae*, measles, mumps and measles vaccination.

Clinical and laboratory findings

Clinical features are described above. Laboratory findings and diagnostic tests are described in the section on investigation of AIHA.

Management

Due to the often transient nature of PCH, initial management is supportive. In the acute phase, intravascular haemolysis can be severe and blood transfusion may be required. P antigen-negative blood is not usually required (Sokol *et al*, 1999). Fever should be managed with anti-pyretics but active cooling should be avoided due to the risk of precipitating haemolysis. Although cold avoidance has been recommended, there is no evidence to support the active warming of patients. Patients can make a good recovery without steroids, which are best reserved for severe or persistent disease. In the setting of life-threatening disease, plasmapheresis may temporarily reduce the haemolysis.

Recommendations (PCH)

- **Encourage cold avoidance and avoid active cooling for fever (2C).**
- **Steroids should only be considered in severe or persistent disease (2C)**

AIHA in pregnancy

Diagnosis of AIHA presenting in pregnancy

AIHA has been estimated to occur in approximately 1 in 140 000 pregnacies (Sokol *et al*, 1982). Diagnosis and investigation for underlying causes should be similar to non-pregnant cases but computed tomography imaging usually avoided and pregnancy-associated causes of haemolysis considered, especially if there is a thrombocytopenia.

Maternal outcome

Maternal outcome is generally good and many cases improve or resolve after delivery.

Fetal outcome

Warm IgG autoantibodies can cross the placenta and cause fetal or post-partum haemolysis analogous to alloimmune haemolytic disease of the newborn (HDN). In the largest series (n = 14), there were 4 spontaneous miscarriages or intrauterine deaths at 4–9 months gestation (Issaragrisil & Kruatrachue, 1983). Although the majority of infants have no sequelae following delivery, the cord DAT is often positive and maternal antibodies may result in anaemia and jaundice in the first few days or late onset anaemia around 4–6 weeks.

Treatment

Most patients receive first line steroids, typically prednisolone 40–80 mg, titrated to response, although high doses may have an effect on the fetus. There is little evidence to guide treatment of steroid-refractory patients. Some patients with CHAD were managed successfully with conservative treatment (e.g. keeping warm, antenatal LMWH and blood transfusion). Some treatments considered acceptable in pregnancy, such as IVIg, azathioprine and (2nd trimester) splenectomy, have been used successfully in non-pregnant AIHA patients. Rituximab can cross the placenta, however, in a series of 20 women who received rituximab during an established pregnancy, all 20 had live births with no neonatal deaths or congenital malformations. (Chakravarty *et al*, 2011).

During pregnancy, serial non-invasive monitoring for fetal anaemia can be achieved by Doppler ultrasound of the fetal middle cerebral artery (Pretlove *et al*, 2009). In the event of worsening fetal anaemia, intrauterine transfusion is unlikely to achieve a sustained correction of anaemia because, unlike HDN, blood is unlikely to be antigen negative for the maternal autoantibody and accelerated destruction could increase fetal bilirubin. Treatment of maternal haemolysis and any underlying cause should be optimised. Maternal IVIg appears to reduce fetal haemolysis in HDN (Porter *et al*, 1997) and may have a role in AIHA with fetal anaemia. Maternal plasma exchange to reduce the circulating autoantibody and early delivery might also be beneficial but studies are needed.

Neonates with early onset anaemia and elevated bilirubin have been successfully treated with phototherapy but sometimes these cases required exchange transfusion. In HDN, early infusion of IVIg (typically 0·5–1 g/kg) reduces the need for exchange transfusion (Gottstein & Cooke, 2003). Late onset anaemia in the infant appears mild and self-limiting in cases of maternal AIHA.

AIHA in pregnancy: Recommendations

- **A positive DAT should prompt taking a history, examination and laboratory testing to exclude AIHA (1C)**
- **Patients should have serial ultrasonography from 20 weeks to assess fetal growth and Doppler ultrasound of the fetal middle cerebral artery to screen for fetal anaemia (2C)**
- **Antenatal care should involve joint haematology and obstetric care with access to a specialist in fetal medicine (1C)**
- **The neonatologist should be informed of the delivery date and the increased risk of neonatal anaemia and hyperbilirubinaemia (1C)**
- **AIHA is a risk factor for thrombosis. Consider antenatal and 6 weeks postnatal prophylaxis in context of other risk factors (2C)**
- **First line treatment (warm AIHA): prednisolone (individualise starting dose based on disease severity and taper to minimum effective dose) (2C)**

- **Second line treatment (warm AIHA): factors influencing treatment include the ability to maintain Hb with transfusional support, stage of pregnancy, primary/secondary AIHA and presence of fetal anaemia (see discussion). Consider IVIg and azathioprine (2C)**
- **Following delivery, test cord blood for DAT. If neonatal jaundice or positive DAT, take a capillary blood sample from the neonate for a full blood count, reticulocyte count, bilirubin, DAT and cross-match (in case exchange transfusion is required) (1C)**
- **Monitor the neonate for anaemia and hyperbilirubinaemia. Management should be similar to that of HDN (1C)**
- **Follow-up the infant for 6 weeks in case late onset anaemia occurs (2C)**

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Author contributions

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All authors have made a full declaration of interests to the BCSH and Task Force Chairs, which may be reviewed on request. The following members of the writing group have no conflicts of interest to declare: QAH, RS, EM, DP, JDG and AH.

Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BCSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BCSH guidelines website at www.bcshguidelines.com. If minor changes are required due to changes in level of evidence or significant additional evidence supporting current recommendations a new version of the current guidance will be issued on the BCSH website.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Systematic review methodology for the 2016 guideline on diagnosis and management of primary autoimmune haemolytic anaemia.

Appendix S2. Expanded version of the 2016 BSH guideline on the diagnosis and management of primary autoimmune haemolytic anaemia.

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